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Letter to the Editor

Refractory focal epilepsy following acute encephalopathy with inflammation-mediated status epilepticus

1. Introduction

Refractory focal epilepsy following acute febrile encephalopathy, also called fever-induced refractory epileptic encephalopathy in school-aged children or febrile infection-related epilepsy syndrome (FIRES), is a topic of great interest and is a newly described condition in Europe and Asia. In a recent review, Nabbout et al. termed this entity "acute encephalopathy with inflammation-mediated status epilepticus (AEIMSE)".[1]

In the last few years, we have diagnosed and treated some patients affected by this condition and showing a similar clinical course.[2,3] In the present report, we review various literature data and add a few concepts regarding the differential diagnosis and the possible role of inflammation and loss of function of the blood-brain barrier (BBB) in the pathogenesis of the disease.

2. Acute and chronic phases

First, we propose to differentiate the disease into 2 main phases: acute and chronic. The acute phase is characterized by the encephalopathy period, in which at least 1 of the following symptoms or signs is continuously present from the onset: seizures, fever, soporous state, confusion, or neurological deficits. The chronic phase, which occurs immediately after the acute phase, is defined as a state of enduring drug-resistant focal epilepsy.[2,3]

In our opinion, recognition of and distinction between the 2 phases is important because these 2 phases require different treatment strategies. Moreover, the duration of the acute phase might better characterize the prognosis in terms of seizure frequency and cognitive and motor outcome; we agree with Nabbout et al. regarding this definition.

3. Differential diagnosis

In all reported patients, the clinical onset resembled an infective cerebral disease, characterized by disturbances of consciousness and multifocal seizures. Differential diagnosis should exclude limbic encephalitis and Alper's disease.[1] A similar stormy onset has been recently identified for other chronic epilepsies, particularly in female patients with protocadherin 19 (*PCDH19*) mutations. In such cases, seizure onset could be related to a febrile illness; status epilepticus at onset is frequent, and cognitive stagnation and deterioration might be evident soon after.[4] Therefore, we suggest that selected female patients with AEIMSE should be tested for point mutations of the *PCDH19* gene; however, most of these children are infants. In addition, most children with FIRES had no reported febrile seizures; almost all had status epilepticus at onset, and the following epilepsy was more severe than that in patients with *PCDH19* mutations, some of whom showed prolonged seizure-free periods during the follow-up.

In most of our patients, brain magnetic resonance imaging (MRI) findings were not informative.[1] However, in a few cases, we found hyperintensity in the peri-insular areas.[2] None of our patients presented with bulging of the mesial temporal structures, T2 hyperintensity, or bilateral temporo-mesial atrophy.[1]

Blood and CSF examination did not reveal infections; however, we found oligoclonal bands and intrathecal IgG synthesis in almost 30% of our patients.[2] This pattern suggests a local B-cell response accompanying an ongoing inflammatory process and a BBB disruption, which might lead to acute seizures in humans and animal models.[5]

4. Therapeutic approach

The reported therapeutic approaches for patients with AEIMSE have not been widely accepted, and different therapeutic strategies have been proposed, most of them with inconstant results. Benzodiazepines, barbiturates, and phenytoin showed poor results, and the use of specific anti-inflammatory medications is controversial; however, a ketogenic diet has been suggested to have a beneficial effect.[1]

Unfortunately, we cannot confirm these results, because the ketogenic diet showed no effect in 2 of our AEIMSE patients. Moreover, we wonder whether patients who are intubated and probably treated with pentothal or propofol have good gastrointestinal transit and absorption. Treatment with methylprednisolone along with intravenous immunoglobulin (IVIG) might improve the outcome both in terms of seizure frequency and cognitive functions,[2,3] particularly if these drugs are used early in the disease course. Future trials with cyclophosphamide or rituximab should be considered to collect sufficient data on their efficacy, because these drugs may modify the disease course.

5. Conclusion

In most patients, neurological symptoms are preceded by various viral infections that are responsible for fever. These viral infections are not directly related to the pathogenesis of AEIMSE but probably activate an immune- or inflammation-mediated condition that determines appearance of seizures and other neurological sequelae.

The characteristics of seizures at the onset (high frequency up to status epilepticus, multifocal predominance, alternating side, and predominantly slow activity on electroencephalograms [EEGs]) appeared to remain unvaried during the chronic phase, although with a milder course; these findings along with the cognitive outcome result in a relatively unique electro-clinical

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picture. Future prospective multicentre studies are required to clarify the pathogenetic role of inflammation and more appropriate therapeutic strategies.

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